

Peters Verny Jones & Schmitt Docket No. 4003.13
Customer No.: 23308

PATENT
Ser. No. 10/664,697

IN THE SPECIFICATION:

Page 23, lines 3, 4 and 5 in Table 2, please amend as shown on the next page.

Table 2

INVENTIVE PEPTIDES - MAP 2 STRUCTURES

	<u>MAP ID NO.:</u>
(NH ₂ -Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₂ - lys-β-ala-COOH	13
(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₂ - lys-lys-(NH ₂)-β-ala-CONH ₂	14
(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₂ -lys-lys-(NH ₂)-β-ala-CONH ₂	15
(NH ₂ -Arg-Gly-Asp) ₂ -lys-β-ala-COOH	16
(CH ₃ CO -Arg-Gly-Asp) ₂ -lys-lys-(NH ₂)-β-ala-CONH ₂	17
(CH ₃ CO -Arg-Gly-Asp) ₂ -lys-lys (NH ₂)-β-ala-COOH	18
(NH ₂ -Arg-Glu-Asp-Val) ₂ -lys-β-ala-COOH	19
(CH ₃ CO-Arg-Glu-Asp-Val) ₂ -lys-lys-(NH ₂)-β-ala-CONH ₂	20
(CH ₃ CO-Arg-Glu-Asp-Val) ₂ -lys-lys-(NH ₂)-β-ala-COOH	21

Peters Verny Jones & Schmitt Docket No. 4003.13
Customer No.: 23308

PATENT
Ser. No. 10/664,697

Page 24, lines 3, 4 and 5 in Table 2 (continued) please amend as shown on the next page.

Table 2 (continued)

INVENTIVE PEPTIDES - MAP 4 STRUCTURES	
	MAP ID NO.:
	(NH ₂ -Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₄ -(lys) ₂ -lys-β-ala-COOH 22
	(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₄ -(lys) ₂ -lys-(NH ₂)-β-ala-CONH ₂ 23
5	(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₄ -(lys) ₂ -lys-(NH ₂)-β-ala-COOH 24
	(NH ₂ -Arg-Gly-Asp) ₄ -(lys) ₂ -lys-β-ala-COOH 25
	(CH ₃ CO-Arg-Gly-Asp) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-ala-CONH ₂ 26
	(CH ₃ CO-Arg-Gly-Asp) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-ala-COOH 27
	(NH ₂ -Arg-Glu-Asp-Val) ₄ -(lys) ₂ -lys-β-ala-COOH 28
	(CH ₃ CO-Arg-Glu-Asp-Val) ₄ -(lys)-lys-lys-(NH ₂)-β-ala-CONH ₂ 29
10	(CH ₃ CO-Arg-Glu-Asp-Val) ₄ -(lys)-lys-lys-(NH ₂)-β-ala-COOH 30

Peters Verny Jones & Schmitt Docket No. 4003.13
Customer No.: 23308

PATENT
Ser. No. 10/664,697

Page 25, lines 3, 4 and 5 in Table 2 (continued) please amend as shown on the next page.

TABLE 2 (continued)

	<u>INVENTIVE PEPTIDES - MAP 8 STRUCTURES</u>	<u>MAP ID NO.:</u>
5	(NH ₂ -Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₈ -(lys) ₄ -(lys) ₂ -lys-β-alanine-COOH	31
	(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-CONH ₂	32
	(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-COOH	33
	(NH ₂ -Arg-Gly-Asp) ₈ -(lys) ₄ -(lys) ₂ -lys-β-alanine-COOH	34
	(CH ₃ CO-Arg-Gly-Asp) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-CONH ₂	35
	(CH ₃ CO-Arg-Gly-Asp) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-COOH	36
	(NH ₂ -Arg-Glu-Asp-Val) ₈ -(lys) ₄ -(lys) ₂ -lys-β-alanine-COOH	37
	(CH ₃ CO-Arg-Glu-Asp-Val) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-CONH ₂	38
	(CH ₃ CO-Arg-Glu-Asp-Val) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-COOH	39
10		

Peters Verny Jones & Schmitt Docket No. 4003.13
Customer No.: 23308

PATENT
Ser. No. 10/664,697

Page 26, lines 3, 4 and 5 in Table 2 (continued) please amend as shown on the next page.

TABLE 2 (continued)
INVENTIVE PEPTIDES - MAP 16 STRUCTURES

		<u>MAP ID NO.:</u>
	(NH ₂ -Gly-Thr-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-β-alanine-COOH	40
5	(CH ₃ CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-CONH ₂	41
	(NH ₂ -Arg-Gly-Glu-Asp)-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-COOH	42
	(CH ₃ CO-Arg-Gly-Asp) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys β-alanine-COOH	43
	(CH ₃ CO-Arg-Gly-Asp) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-CONH ₂	44
	(NH ₂ -Arg-Glu-Asp-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys β-alanine-COOH	45
10	(CH ₃ CO-Arg-Glu-Asp-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-CONH ₂	46
	(CH ₃ CO-Arg-Glu-Asp-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-COOH	47
	(CH ₃ CO-Arg-Glu-Asp-Val) ₁₆ -(lys) ₈ -(lys) ₄ -(lys) ₂ -lys-lys-(NH ₂)-β-alanine-COOH	48

IN THE SPECIFICATION:

Please amend the paragraph on page 57, line 16 to page 58, line 4 as shown:

EXAMPLE 1

PREPARATION OF A MAP4



(a) The MAP4 peptide, (NH₂-Gly-Thr-Pro-Gly-Pro-Gln-Ile-Ala-Gly-Gly-Gln-Arg-Gly-Val-Val)₄-(Lys)₂-Lys-β-Ala-COOH was assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling was accomplished with the specific amino acid sequence of the MAP4 peptide. Coupling of all other Fmoc amino acids for the desired sequence was accomplished using 3 equivalents of 1-Hydroxybenzotriazole (HOBT) and 3 equivalents of 1,3 diisopropylcarbodiimide (DIC). Coupling times of about 120 min were employed. After each coupling the protected peptide Wang resin intermediate was washed as before with 3 volumes each of DMF, methanol and DCM. The completeness after the coupling and cleavage reactions were monitored by the Kaiser Ninhydrin test. Following the addition of the last Fmoc-residue and following the deprotection of the Fmoc-group, the peptide Wang resin intermediates was again washed with DMF, methanol and DCM, then air dried.

Please amend the paragraph on page 61, lines 12-19 as shown:

EXAMPLE 2

PREPARATION OF A MAP2

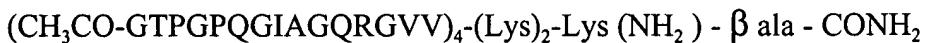
(NH₂-GTPGPQGIAGQRGVV)₂-Lys-β ala-COOH

(a) The MAP2 peptide, (NH₂-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val)₂-Lys-β-Ala-COOH was assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling was accomplished as described in Example 1, but with the specific amino acid sequence of the MAP4 peptide.

Please amend the paragraphs on page 63, lines 3-31 as shown:

EXAMPLE 3

PREPARATION OF A MAP4



(a) The MAP4 peptide, (CH₃CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val)₄-(Lys)₂-Lys- (NH₂)- β-Ala-CO NH₂ was assembled on a Fmoc-β-Ala Wang resin. A procedure similar to that of Example 1(a) was used. An additional lysine group was added to the Fmoc-β ala resin. The N-terminal group was protected by acetylation. The purified MAP4 produces satisfactory amino acid analysis. MAP 4 is then coupled with ePTFE.

(b) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

(e) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 3(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Gln-Arg-Gly-Ile-Ala-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a

stochiometrically effective amount of WQPPRADI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

Please amend the paragraphs on page 65, lines 1-26 as shown:

(a) The MAP2 peptide, (CH₃CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val)₄-(Lys)-Lys(NH₂)-β-ala-COOH is assembled on a Fmoc-β-Ala Wang resin. A procedure similar to that of Example 3(a) is used. An additional lysine group is added to the Fmoc-β ala resin. The N-terminal group is protected by acetylation. The purified MAP4 produces satisfactory amino acid analysis. MAP 4 is then coupled with ePTFE.

(b) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of RGD (SEQ ID NO: 2). Improved cell adhesive and cell proliferation are observed.

(c) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of YIGSR (SEQ ID NO: 5). Improved cell adhesive and cell proliferation are observed.

(d) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of REDV (SEQ ID NO: 3). Improved cell adhesive and cell proliferation are observed.

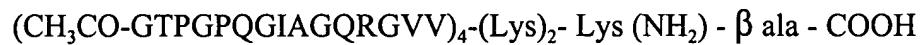
(e) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of SIKVAV (SEQ ID NO: 6). Improved cell adhesive and cell proliferation are observed.

(f) Similarly, Example 4(a) is repeated except that Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val (SEQ ID NO: 1) in MAP is replaced with a stoichiometrically effective amount of WQPPRAPI (SEQ ID NO: 4). Improved cell adhesive and cell proliferation are observed.

Please amend the paragraph on page 66, lines 24-31 as shown:

EXAMPLE 5

PREPARATION OF A MAP4

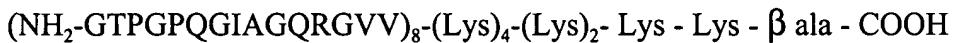


(a) A similar procedure as in Example 4 (a) was used in the preparation of $(\text{CH}_3\text{CO}-\text{Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val})_4-(\text{Lys})_2-\text{Lys}(\text{NH}_2)-\beta\text{-Ala-COOH}$. An additional lysine group was added to the Fmoc- β -ala resin. The purified MAP4 produces satisfactory amino acid analysis. The MAP was then coupled with ePTFE.

Please amend the paragraphs on page 68, lines 15-29 as shown:

EXAMPLE 6

PREPARATION OF A MAP8



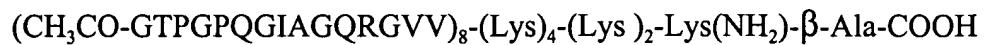
(a) A procedure similar to that found in Example 1 (a) is used to prepare MAP peptide, $(\text{NH}_2\text{-GTPGPQGIAGQRGVV})_8\text{-}(\text{Lys})_4\text{-}(\text{Lys})_2\text{-Lys-}\beta\text{-Ala -COOH}$ assembled on a Fmoc- β -Ala Wang resin. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP peptide produces satisfactory amino analyses.

A similar procedure as in Example 4 is used in the preparation of $(\text{CH}_3\text{CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly-Ile-Ala-Gly-Gln-Arg-Gly-Val-Val})_8\text{-}(\text{Lys})_4\text{-}(\text{Lys})_2\text{-Lys(NH}_2\text{)-}\beta\text{-Ala-COOH}$. An additional lysine group is added to Fmoc- β -Ala Wang resin. The purified MAP8 produces satisfactory amino analysis. The MAP is then coupled with ePTFE.

Please amend the paragraph on page 70, lines 13-20 as shown:

EXAMPLE 7

PREPARATION OF A MAP8

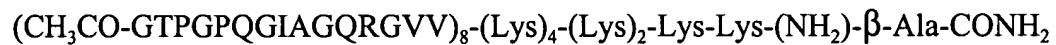


(a) A similar procedure as in Example 4 is used in the preparation of $(\text{CH}_3\text{CO}-\text{Gly-Thr-Pro-Gly-Pro-Gln-Gly -Ile-Ala-Gly-Gln-Arg-Gly-Val-Val})_8-(\text{Lys})_4-(\text{Lys})_2-\text{Lys-Lys}(\text{NH}_2)-\beta\text{-Ala-COOH}$. In this case, the MAP has eight arms. The purified MAP8 produces satisfactory amino analysis. MAP is then coupled with ePTFE as described herein.

Please amend the paragraph on page 72, lines 4-16 as shown:

EXAMPLE 8

PREPARATION OF



(a) The MAP8 peptide, $(\text{CH}_3\text{CO}-\text{Gly-Thr-Pro-Gly-Pro-Gln-Gly -Ile-Ala-Gly-Gln-Arg-Gly-Val-Val})_8-(\text{Lys})_4-(\text{Lys})_2-\text{Lys-Lys}(\text{NH}_2)-\beta\text{-Ala-COOH}$ is assembled on a Fmoc- β -Ala Wang resin. Following deprotection of the Fmoc- β -Ala resin, coupling is accomplished as described in Example 1, but with the specific amino acid sequence of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP8 produces satisfactory amino acid analysis. The MAP is then coupled with ePTFE as described herein.

Please amend the paragraph on page 74, lines 3-15 as shown:

EXAMPLE 9 (A MAP 16)

PREPARATION OF

(CH₃CO-GTPGPQGIAGQRGVV)₁₆-(Lys)₈-(Lys)₄-(Lys)₂-Lys-Lys(NH₂)-β-Ala-COOH

(a) The MAP16 peptide, (CH₃CO-Gly-Thr-Pro-Gly-Pro-Gln-Gly Ile-Ala-Gly-Gln-Arg-Gly-Val-Val)₁₆-(Lys)₈-(Lys)₄-(Lys)₂- Lys-Lys(NH₂)-β-Ala-COOH is assembled on a Fmoc-β-Ala Wang resin. Following deprotection of the Fmoc-β-Ala resin, coupling is accomplished as described in Example 1, but with the specific amino acid sequence of the MAP peptide. After the final amino acid residue is added and the Fmoc deprotection group removed, the peptide Wang resin is washed with DMF, methanol and DCM. Cleavage of the protecting groups and coupling reactions are also monitored using the Kaiser Ninhydrin test. The purified MAP4 produces satisfactory amino acid analysis.